Seizure 20 (2011) 280–284

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Suicidal risk and suicide attempts in people treated with antiepileptic drugs for epilepsy

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ARTICLE INFO

Article history:
Received 5 October 2010
Accepted 14 December 2010

Keywords:
Suicidality
Antiepileptic drugs
Epilepsy
Suicidal risk
Suicide attempts
Depressive disorders

ABSTRACT

Objective: To determine whether antiepileptic drugs constitute in themselves an independent risk factor for suicidality in patients with epilepsy.
Methods: One hundred and thirty one patients with epilepsy were recruited and followed-up during 5 years. A detailed medical history, neurological examination, EEGs, Mini-International Neuropsychiatric Interview, executive function, and MRI were assessed. Systematically collected data were used to assess suicidality. Multiple regression analysis was carried out to examine predictive associations between clinical variables, psychiatric disorders, antiepileptic drugs and suicidality.
Results: We identified two AEDs related with suicide attempts (PHB and LTG) and four with suicidal risk: PHB, PRM, PHT and LTG, but the increased of risk diminished or disappeared when psychiatric comorbidity and other well established risk factors for suicidality were analyzed. We found a significant proportion of patients with depressive episodes associated with Topiramate, Phenitoin, Phenobarbital and Lamotrigine.
Conclusion: Antiepileptic drugs probably do not have an impact on suicidality.

1. Introduction

On January 31, 2008, the US Food and Drug Administration (FDA) issued an alert that a meta-analysis had found a statistically significant 1.80-fold increased risk for suicidality associated with all antiepileptic drugs (AEDs).[1] Various potential problems with the meta-analysis have been identified: first of all, adverse event data were used rather than systematically collected data, secondly, each of the 11 drugs, grouped together as a single class of AEDs, has different mechanisms of action and different relative risks, some of which were not statistically significant and several were smaller than one, suggesting that these drugs should not be grouped in a single class for this purpose, thirdly, the risk of adverse effects from uncontrolled seizures, almost certainly, outweighs the risk of suicidality.[2–8] This is very important taking into account that AEDs are not the only option for the treatment of psychiatric disorders or pain, but currently there is no alternative pharmacological treatment for epilepsy. Therefore, assessment of the risk–benefit balance for the treatment of epilepsy may be more important than for disorders for which there are alternative treatments and AEDs are prescribed. Although the issue of suicidality with AEDs is controversial; the adverse effects of failing to control epilepsy are not.[9–13] Considering that serial systematic data collection of suicidality is the only way to eliminate the biases already discussed, we conducted the present prospective study using validated instruments. We expect that the information collected in the current study will help us determine the validity of the FDA alert.

2. Methods

We conducted a prospective cohort study including 131 patients with epileptic seizures when diagnosed was first established in epilepsy section of our hospital.

The inclusion criteria for epilepsy were based on the ILAE classification,[14] and all patients were followed in our unit for at least 5 years. Exclusion criteria included clinical illnesses other than epilepsy (cerebro-vascular accident, brain tumor, asthma, severe coronary disease, Migraine, Multiple Sclerosis, Myasthenia Gravis, mental retardation, Mild Cognitive Impairment, Dementia

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doi:10.1016/j.seizure.2010.12.010

and Parkinson disease) and antihistamine or alcohol consumption within 72 h prior to the psychiatric evaluation.

2.1. Subjects

After giving informed consent, the patients were assigned to non-aleatorized treatment with AED according to the specific epileptic syndrome and seizure response. All patients were followed in the outpatient clinic of a tertiary center (Epilepsy Section, Institute of Neurology, Havana, Cuba), from March 2004 to December 2009. The description of the epileptic syndromes and the subjects who participated in the present study appear in Table 1. Thirty-one patients were excluded: 9 because they did not complete the follow-up scheme, 16 because a secondary cause for epilepsy was diagnosed (9 patients had a cerebrovascular event, 7 patients had brain tumor), the remaining 6 patients refused to participate and to answer the questionnaires. All patients are evaluated with electroencephalogram and Magnetic Resonance Imaging (MRI).

2.2. Procedures

2.2.1. Neurological investigation

The neurological evaluation was conducted at baseline and during follow-up (every 3 months). The neurological investigation consisted of a detailed medical history, neurological examination and serials electroencephalogram (EEGs) and MRI. When temporal lobe epilepsy was suspected we estimate left or right epileptogenic zone taking into account clinical, neuropsychological, EEG, and MRI features. At a minimum, clinicians obtained the following clinical data: (1) current or past history of the main depressive and anxiety disorders (e.g., major depressive disorder, generalized anxiety disorder, panic disorder); (2) current or past history of suicidal attempts both during the interictal and postictal periods; and (3) family psychiatric history of mood disorders and suicidal behavior. When we identified current psychiatric symptoms or suicidality, we referred the patient to a mental health care professional for treatment.

2.2.2. Psychiatric evaluation

We recorded clinical and sociodemographic data such as years of education, marital status, economic difficulties, labor market status, annual income, absences from work due to illness, as well as personality disorders. The same psychiatrists (S.G.B. and A.G.E.) evaluated each subject during enrolment in the study (at baseline) using a structured interview (Mini-International Neuropsychiatric Interview [MINI]),[15] and conducted the follow-up looking for psychiatric complications or suicide attempts. The mood and anxiety disorder modules of the MINI were used to identify current and past rates of depression and anxiety. The mood disorders module of the structured clinical interview for DSM-IV-R Axis I Disorders—Research Version (SCID-I) was used also to obtain data on past major depressive episodes.[16]

After initial evaluation the psychiatrists established suicidal risk, and current and past depressive disorder for every patient according to the suicidal risk scale, MINI and SCID-I. For this study, full scale SR scores greater than 7 indicated suicidal risk.

For the purposes of this study, suicidal risk (SR), depressive disorder and other psychiatric complications were assessed with the appropriate module of the MINI also every 3 months or when patients referred symptoms suggesting psychiatric complications.

2.2.2.1. Evaluation of psychiatric conditions in the relatives. When family history of psychiatric conditions was reported we asked the patients to bring an appropriate certificate signed by her or his psychiatrist. Only information about first and second degree relatives was accepted.

2.2.3. Neuropsychological evaluation

Each subject received a comprehensive neuropsychological assessment using neuropsychological instruments previously validated in Cuba by M.E.G.

2.3. Statistical analysis

Logistic regression was used to examine whether AEDs affected suicidal risk, suicide attempts and depressive episodes. For these purposes, we associated AEDs regiment of treatment with psychiatric complication only if AEDs had been used for at least a week. To determine the relationship between suicidal risk, suicide attempts, depressive disorders and treatment with AED, the psychiatric complications (depressive disorders and suicide attempts) should be documented during the follow-up and should not be present at baseline or the suicidal risk scale score increased over baseline score during treatment. We considered suicidal risk in patients scoring over 7 points on the suicidal risk scale.

A second analysis was performed excluding the possible influence of psychiatric disorders on suicidal risk and suicide attempts. For this purpose we conducted a logit regression for categorical (binary) dependent variables (depressive disorders, suicidal risk, and suicide attempts) and a list of predictor variables (AEDs). We used the generalized linear models to perform stepwise and best subset selection of predictors in ANCOVA-like designs. This statistical analysis reports also the covariance matrix of parameter estimates and classification odds ratios. To carry out this type of analysis depressive disorders, suicidal risk and suicide attempts were analyzed as dependent variables and each AED as an independent variable, whereas the following covariates were controlled: uncontrolled seizures, psychiatric co morbidity and past history of suicidal behavior or psychiatric disorders were controlled.

We considered both "current episode of psychiatric disorders" and "previous history of psychiatric episodes" when documented in the clinical records. Multiple regression analysis was conducted to examine the role of AEDs on suicide attempts when other risk factors for suicide in patients with epilepsy were present, such as executive dysfunction, gender, depressive disorder, familiar history of psychiatric diseases, disease duration, left temporal lobe epilepsy, and postictal psychosis

Table 1
Demographic characteristics in patients with epilepsy.

Epileptic syndrome $n = 131$	
Temporal lobe epilepsy	101 (77.1)
Juvenile myoclonic epilepsy	24 (18.3)
Cryptogenic frontal lobe epilepsy	4 (3.1)
Cryptogenic parietal lobe epilepsy	2 (1.5)
Gender females/males n (%)	71/60 (54.2/45.8)
Age (years)	Mean ± SD 41. 4 ± 14,3 (range: 18–78)
Age at onset of epilepsy (years)	Mean ± SD 24.9 ± 16.9 (range: 6.5–55)
Disease duration (years)	Mean ± SD 19.7 ± 13.6 (range: 1–33)
Localization of epileptiform discharges	
Restricted to temporal lobe	80 (61.1)
No epileptiform discharges	21 (16.3)
Generalized epileptiform discharges	24 (18.3)
Fronto-parietal discharges	6 (4.5)
Average full scale IQ	Mean ± SD 93.5 ± 7.5 (range: 87–99)
Education	
High school and/or university	126 (96.2)
<High school	5 (3.8)

3. Results

Patients' demographic and clinical characteristics appear in Table 1.

Table 2
Monotherapy regimen of treatment in our series.

Antiepileptic drugs	*N* (%)	Range of doses
Phenobarbital (PHB)	15 (11.5)	3–5 mg/Kg/daily
Phenytoin (PHT)	15 (11.5)	3–8 mg/Kg/daily
Carbamazepine (CBZ)	38 (29)	10–30 mg/Kg/daily
Valproate (VPA)	25 (19.1)	23–60 mg/Kg/daily
Lamotrigine (LTG)	14 (10.7)	0.8–7.2 mg/Kg/daily
Topiramate (TPM)	12 (9.2)	3–6 mg/Kg/daily
Primidone (PRM)	12 (9.2)	5–7.8 mg/Kg/daily

Table 3
Suicidal risk and suicide attempts in our patients during enrollment and follow up.

Suicidal risk and suicide attempts in the study *n* (%)	
Suicidal thoughts	70 (53.4)
Suicide attempts before epilepsy diagnosed‡	4 (3.1)
Suicide attempts after diagnosis of epilepsy	38 (32.8)
Suicidal risk initially (with at least a week under treatment)	48 (36.6)
Suicidal risk when psychiatric complication emerged	68 (60.1)

± All of them have experienced depressive episodes.

3.1. Monotherapy in our series (Table 2)

Antiepileptic drugs and their respective dosages are shown in Table 2. Old and new antiepileptic drugs were used.

3.2. Risk for suicide and suicide attempts in our series (Table 3)

Forty eight of 131 individuals (36.6%) scored >7 on the SR module of MINI when they were enrolled in the study and after at least one week under treatment, but this number of patients increased up to 68 (60.1%) when psychiatric complications emerged. Thirty-eight patients (32.8%) had attempted suicide during the follow-up; nevertheless, 4 of 131 patients (3.1%) had at least one suicide attempt before epilepsy was diagnosed, hence they had not received antiepileptic treatment yet (all of them had experienced depressive episodes). No information was available regarding the severity of these suicide attempts. More than fifty percent of patients experienced suicidal thoughts (53.4%).

3.2.1. Suicide attempts, suicidal risk and depressive disorder according to antiepileptic drug on monotherapy regimen of treatment (Table 4)

The patients in the table represent patients with new symptoms ($n = 20$) and who developed worsening symptoms ($n = 28$). The number of patients with suicidal risk was greater for patients treated with PRM (primidone), LTG (Lamotrigine), PHB (phenobarbital) and Phenitoin (PHT). Suicide attempts were reported in 5 of 15 patients treated with PHB (33.3%), 5 of 15 patients treated with PHT (33.3%), 8 of 14 individuals treated with LTG (57.1%). The probability of suicide attempts was greater in patients treated with PHB (OR 1.2; CI (2.3–3.4) and LTG (OR 6.2; CI (2–7.8)). Patients who were under treatment with the following AEDs (PHB, PHT, TPM) had an increased probability to develop depressive episodes [OR > 1 and valid CI].

Table 5
Suicidal risk and suicide attempts according to antiepileptic drugs when personal and family history of psychiatric disorders were statistically controlled variables.

Medication	OR (CI)
Phenobarbital (PHB)	0.9 (0.1–5.9)
Phenytoin (PHT)	1.2 (0.5–1.9)
Carbamazepine (CBZ)	0.1 (0.1–1.2)
Valproate (VPA)	0.5 (0.1–0.6)
Lamotrigine (LTG)	0.5 (0.7–1.9)
Topiramate (TPM)	2.9 (0.9–3.2)
Primidone (PRM)	1.1 (0.8–4.9)

Table 6
Contribution of each factor affecting the risk for suicide and suicide attempts in patients with epilepsy taking antiepileptic drugs.

Factors affecting the risk for suicide and suicide attempts	Suicide attempts OR (IC)	Suicidal risk OR (IC)
Depression (current episode)	3.3 (1.1–46.1)*	3.4 (1.9–23.4)***
Recurrent depressive disorder	6.7 (2–41.1)*	7.9 (2.1–29.6)***
Familiar history of psychiatric disorders	1.8 (1.2–3.6)	2.1 (1.9–4.5)**
Executive dysfunction	4.8 (1.5–15.2)*	5.6(2.8–7.9)**
Gender (female)	0.5 (0.8–2.4)	0.9 (0.2–0.7)
Disease duration	0.9 (1.7–2.2)*	0.3 (1.01–3.7)*
Perictal psychosis	2.1 (2.1–8.7)*	2,4 (3.2–9.7)**

Examination for suicide attempts (logistic regression): OR 2.2 IC (1.1–3.7) Chi^2 (11) = 37.6 $p = 0.0000$. Assessment for suicidal risk (logistic regression): OR 1.8 IC (1.3–3.4) Chi^2 (11) = 41.3 $p = 0.0000$.
* Mean $p \leq 0.05$ but >0.01.
** $p = 0.01$.
*** $p < 0.01$.

3.2.2. The effect of AEDs on suicidality when comorbidity of epilepsy with depressive disorders was statistically controlled (Table 5)

When variables such as family history of depressive disorders and current depressive episodes were controlled the regression model did not show statistically significant differences by subgroup of antiepileptic drugs analyzed (i.e., OR < 1 or 95% CI = 1).

3.3. Risk factors for suicide attempts and suicidal risk in our series: the contribution of antiepileptic drugs when others risk factors are present (Table 6) (multivariate analysis)

The overall regression model explained the significant proportion of variance for both suicide risk and suicide attempts. There was a 1.8-fold increase in the risk for suicide in those with a family

Table 4
Suicide attempts, suicidal risk and depressive disorder according to antiepileptic drug on monotherapy regimen of treatment.

AED	Depressive disorder			Suicidal risk			Suicide attempts		
	OR (CI)	Yes (%)	No (%)	OR (CI)	Yes (%)	No (%)	OR (CI)	Yes (%)	No (%)
PHB	1.3 (1.1–1.9)	5 (33.3)	10 (66.7)	1.9 (1.1–2.9)	7 (46.6)	8 (53.4)	1.2 (2.3–3.4)	5 (33.3)	10 (66.7)
PHT	2.1(1.2–4.3)	3 (20)	12 (80)	1.9 (1.1–2.9)	7 (46.6)	8 (53.4)	1.2 (2.3–3.4)	5 (33.3)	10 (66.7)
CBZ	1.3 (0–12)	7 (18.4)	31 (81.6)	2 (0–14)	9 (23.7)	29 (76.3)	3 (0–26)	9 (23.7)	29 (76.3)
VPA	0.4 (0.2–2.5)	6 (24)	19 (76)	2.3 (0.8–5)	8 (32)	17 (68)	6.2 (1–7)	8 (32)	17 (50)
LTG	0.2 (0.3–7.3)	4 (28.6)	10 (71.4)	7.2 (2.3–14.3)	7 (50)	7 (50)	6.2 (2–7.8)	8 (57.1)	6 (42.9)
TPM	1.5 (1.2–2.3)	4 (33.3)	8 (67.7)	1.5 (1–3.4)	4 (33.3)	8 (67.7)	3.1 (2–3.9)	1 (8.3)	11 (91.7)
PRM	2.9 (2.1–1.9)	4 (33.3)	8 (67.7)	1.9 (1.2–2.1)	6 (50)	6 (50)	1.4 (1.3–1.5)	2 (16.6)	10 (83.3)

% are referred to total patients with each drug on monotherapy regimen. The following covariates were controlled uncontrolled seizures, psychiatric comorbidity and past history of suicidal behavior or psychiatric disorders were controlled. The patients in the table represent patients with new symptoms ($n = 20$) and who developed worsening symptoms ($n = 28$).

history of psychiatric disease, longer disease duration, current and past history depressive episode, executive dysfunction, pericta psychosis and female gender [95% IC (1.3–3.4) Chi^2 (11) = 41.3 $p = 0.0000$]. The model also explained a 2.2-fold increase in the risk for suicide attempts [OR 2.2 IC (1.9–3.9) Chi^2 (11) = 37.6 $p = 0.0000$]. AEDs were not associated with an increase of the suicidal risk or suicide attempts.

4. Discussion

The analysis of suicidality in the present sample could be biased due to the excessive representation of patients predisposed biologically to suicide such as patients with temporal lobe epilepsy,[16–33] but it adequately represented the population of people with epilepsy in our clinical setting. We did not include patients with other secondary causes for epilepsy (i.e., cerebrovascular accident, tumors, vascular malformations, central nervous system infection and trauma) to avoid an even more complicated analysis of the complex relationship among epilepsy, AEDs and suicidality.

In the present study, the data concerning rate of suicidal risk and suicide attempts were registered systematically. For this purpose we used the standardized MINI. We also analyzed each AED separately; the effects from uncontrolled seizures, psychiatric comorbidity and past history of suicidal behavior or psychiatric disorders were controlled. The use of systematically collected data, rather than adverse event data on suicidality, is one of the strengths of our study for several reasons. Systematically collected data is obtained from reports of the event at hand using a validated scale (MINI in our study). The use of a validated scale limited the number of patients reporting more adverse events when compared to patients taking a placebo,[3,4] and thus, we avoided the phenomenon referred to as reporting bias. The FDA accepts systematically collected data as the primary endpoint in a clinical trial.

We identified two AEDs related with suicide attempts (PHB and LTG) and four AEDs related with suicidal risk (PHB, PRM, TPM and LTG), but such risk diminished or disappeared as psychiatric comorbidity and other well established risk factors for suicidality were statistically controlled. These results suggest that personal or familiar history of psychiatric disorders and/or current depressive episodes play a pivotal role in suicidal behavior in patients with epilepsy. The relevant message is that previous psychiatric history and family psychiatric history are the major determinants for the development of suicidal ideation and suicidal attempts rather than the AED.

The incidence of psychiatric disorders in patients taking AEDs as previously reported[26,33–36] was verified in our study. A subgroup of patients who were under treatment with PHB, PHT, LTG and TPM displayed an increased susceptibility to develop depressive episodes [OR > 1 and valid CI]. The previous studies could not rule out the contribution of other factors such as family history of psychiatric disorders or past psychiatric disorders as we were able to do.[1,31,32] We mention these studies because psychiatric disorders, which can potentially facilitate the development of suicidal attempts and increase the suicidal risk, have been associated with PHB and PRM (among the older AEDs), and with vigabatrin, levetiracetam, TPM, and zonisamide (among second-generation AEDs).[33,34] Still, the incidence of suicidal behavior resulting from AED exposure itself remains unknown, as most published data group all psychiatric adverse events together,[33,34] rather than reporting suicidality by itself, and those studies reporting suicidality have not adjusted for prior episodes of depression and prior suicidality.[1,31–33] In the present study, we independently investigated depressive disorder and other psychiatric complications in patients with epilepsy and adjusted for an increase of suicidality for AEDs and for previous depressive episodes. Only four out of 131 patients reported attempting suicide before being treated with AEDs; all of them had previously experienced depressive episodes.

4.1.1. ADEs and psychiatric comorbidity in patients with epilepsy

Our results mirror other case studies of patients treated with AEDs. Trimble et al.[33] investigated psychiatric adverse events in patients with epilepsy taking AEDs and found that nearly two-thirds of the patients had a psychiatric history with a strong association between the type of past psychiatric illness and the emerging illness. In studies conducted with patients treated with Levetiracetam, a family history of psychiatric disorders was a significant predictor for the development of psychiatric symptoms.[35,36] Among patients treated with Topiramate, 23% were found to exhibit psychiatric symptoms. The risk was greater in patients with a family psychiatric history and in those with a previous psychiatric history.[33,34] Therefore, a family history of psychiatric disorders is associated with an increased risk to develop psychiatric disorders, predominantly depression, while taking AEDs. This may reflect the natural course of an underlying recurrent psychiatric illness with no effects from AEDs, or it could suggest that AEDs lower the threshold for manifesting psychiatric symptoms in individuals who are vulnerable because of a history of psychiatric disorders.

Considering the logistic regression model, suicide risk and suicide attempts were higher than the individual risks for each variable, suggesting that these factors share a common pathogenic mechanism in suicide risk.

The association found among family history of psychiatric diseases, current depressive episode, duration of epileptic diseases, pericta psychosis, executive dysfunction, gender, suicide attempts, and suicide risk in patients with epilepsy strengthens the idea of the existence of a biological basis underlying epilepsy and suicidal risk.In conclusion, the relationship between suicidality and epilepsy is a complex, multifactorial issue, and AEDs probably have little or no impact. Serial systematic data collection of suicidality did not suggest that AEDs play an important role in suicidality.

Conflict of interest

None declared.

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